HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For

CHLORINATED PYRIDINE CATEGORY

Prepared by:

The Dow Chemical Company

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TEST PLAN FOR CHLORINATED PYRIDINE CATEGORY

PLAIN ENGLISH SUMMARY

This test plan addresses the chemical category of chlorinated pyridines, which includes 2,3,4,5,6-pentachloropyridine (CAS No. 2176-62-7), 3,4,5,6-tetrachloro-2-pyridine carbonitrile (CAS No. 17824-83-8), 3,6-dichloro-2-trichloromethylpyridine (CAS No. 1817-13-6), 2-chloro-5-trichloromethylpyridine (CAS No. 69045-78-9), chloropyridine derivatives (CAS No. 68412-40-8), and methyl chloropyridine derivatives (CAS No. 70024-85-0). In addition, for purposes of enriching the database for this category, 2,3,5,6-tetrachloropyridine (CAS No. 2402-79-1) has been included. Existing data are summarized. No additional data are needed under the HPV Challenge Program.

EXECUTIVE SUMMARY

The Dow Chemical Company hereby submits for review and public comment the test plan for the chlorinated pyridine category under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of The Dow Chemical Company to use a variety of existing data and scientific judgment/analyses to adequately characterize the SIDS (Screening Information Data Set) human health, environmental fate and effects, and physicochemical endpoints for this chemical stream.

Chemical Category: Chlorinated Pyridines

1. Identification of category and Rationale for Use

The Chlorinated Pyridines category is defined as a structurally related group of chlorinated pyridine molecules, and includes several process streams of related process byproducts. All of these chemicals have a common Structure-Activity-Relationship (SAR) to serve as the technical basis for the category under the EPA HPV Challenge Program.

In the EPA Guidance Document entitled Development of Chemical Categories in the HPV Challenge Program, under Section II entitled Definitions, the following information is given:
"A chemical category, for the purposes of the Challenge Program, is a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. These structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and human health effects. The similarities may be based on the following:

- a common functional group[e.g., aldehyde, epoxide, ester, etc.]; or
- the likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals [e.g., the "family approach" of examining related chemicals such as acid/ester/salt]; and
- an incremental and constant change across the category [e.g., the dimethylene group difference between adjacent members of the alpha-olefins]-"

The Chlorinated Pyridine Category proposed herein complies with the EPA definition of an acceptable Category based on all three criteria cited above, namely

[a] the sharing of a common functional group (all chlorinated derivative of a pyridine backbone),
[b] the likelihood of common precursors and/or breakdown products via physical or biological processes, which result in structurally similar chemicals, and
[c] incremental changes in chemical structure as one progresses from lower to higher states of chlorination of the pyridine backbone.

All category members (except 2,3,4,5,6-pentachloropyridine, which qualifies as a production chemical) should be regarded as site-limited intermediates, based on the extremely limited potential for exposure during manufacturing, transport, consumption and use.

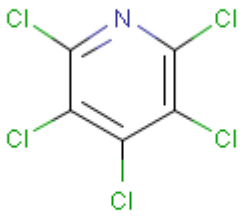
These chemicals/process streams are used in other site manufacturing processes or are converted to feedstock for chlorine production, with no sales or off-site transport, and thus little potential for exposure of non-employee populations.

Although the chemicals are isolated during manufacture, the potential for employee exposure is similarly low, usually only during maintenance or site-limited transport procedures (see the specific chemical for more detail).

The group consists of molecules with a pyridinyl backbone, with varying levels of chlorination; some have other chemical moieties in addition to the chlorine atoms (e.g., methyl groups); two of the category members are process streams of mixed chlorinated pyridines.

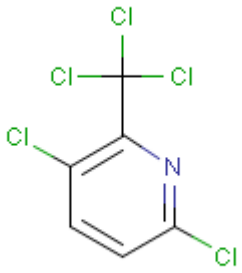
The chemicals included in this category are:

A. 2,3,4,5,6-Pentachloropyridine
CAS # 2176-62-7



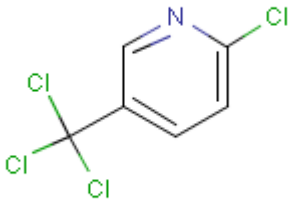
This material is a production chemical, under the conditions of the US EPA HPV Challenge Program.

B. 3,6-Dichloro-2-trichloromethylpyridine
CAS # 1817-13-6



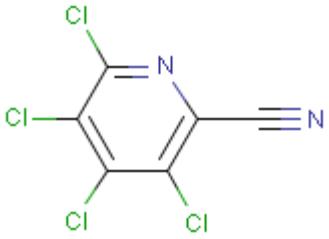
Potential for employee exposure to this material is low: the material is totally contained via hard piping and pumped to a reactor for pesticide production; lines are opened periodically for sampling, or for maintenance as required; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, eye protection, and respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance.

C. 2-Chloro-5-trichloromethylpyridine
CAS # 69045-78-9



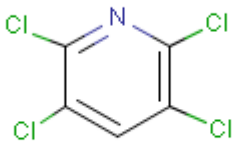
Potential for employee exposure to this material is low: the material is totally contained via hard piping and pumped to a reactor for pesticide production; lines are opened periodically for sampling, or for maintenance as required; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, eye protection, and respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance.

D. 3,4,5,6-Tetrachloro-2-pyridine carbonitrile
CAS # 17824-83-8



Potential for employee exposure to this material is low: the material is totally contained via hard piping and pumped to a reactor for pesticide production; lines are opened periodically for sampling, or for maintenance as required; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, eye protection, and respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance.

E. 2,3,5,6-Tetrachloropyridine
CAS # 2402-79-1



Potential for employee exposure to this material is low: the material is totally contained via hard piping and pumped to a reactor for pesticide production; lines are opened periodically for sampling, or for maintenance as required; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, eye protection, and respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance.

F. Chloropyridine derivatives
CAS # 68412-40-8

No structure is included for this chemical mixture, since it is a process stream composed of the following components:

Pentachloropyridine	3.3%
2,3,4,6-Tetrachloro-5-pyridinecarbonitrile	0.1%

Hexachlorobenzene	16.2%
Pentachloroethynylpyridine	28.1%
3,4,5,6-Tetrachloro-1,2-benzenedicarbonitrile	0.8%
2,4,5,6-Tetrachloro-1,3-benzenedicarbonitrile	1.4%
Trichloroethylenetetrachloropyridine isomers (3 isomers)	9.5%
Pentachloro(trichloroethenyl)-benzene	1.0%
1,2,4-Trichloro-5-[(chloropheny)thio]benzene	0.2%
Tetrachlorodihydromethylbenzo(A)carbazole isomers (3 isomers)	0.9%
Hexachlorobipyridylene Isomers/Derivatives (3 isomers/derivatives)	0.5%
Perchlorovinylcyanopyridine isomers (2 isomers)	0.7%
4-[p-bis(2-hydroxyethylamino]phenyl-1-bromoisoquinoline	2.0%
Heptachlorobipyridylene Isomers/Derivatives (2 isomers/derivatives)	1.1%
Octachlorobipyridylene Isomers/Derivatives (5 isomers/derivatives)	6.7%
Trichlorovinyltetrachloroethynylpyridine	9.8%
Hexachlorobipyridylene Isomers/Derivatives (9 isomers/derivatives)	16.5%
Nonachlorophenylpyridine	0.2%
Octachloronaphthalene	0.7%
Heptachlorobipyridylene Isomer or Derivative	0.3%
Irieol	0.4%

It should be noted that the percentages indicated above represent data gathered at one point in time, and vary with the time the process stream was sampled.

Potential for employee exposure to this material is low: the material is transferred to a tank car for transport to a reactor on site 3-4 times per week; recommended personal protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, eye protection, and respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance.

G. Methyl chloropyridine derivatives
CAS # 70024-85-0

No structure is included for this chemical mixture, since it is a process stream composed of the following components:

1,2,3,4,11-Pentachloro-8-(trichloromethyl) dipyrioimidazolium tetrachloroferrate and process contaminants	46%
Chlorinated pyridines	31%
Ferric chloride	15%
Chlorinated bipyridines	6%
Chlorohydrocarbons	2%

It should be noted that the percentages indicated above represent data gathered at one point in time, and vary with the time the process stream was sampled.

Potential for employee exposure to this material is low: the material is totally contained via hard piping and pumped to a reactor for burning/HCl reclamation; lines are opened every two weeks for sampling, or for maintenance as required; recommended personal

protective equipment comprises full chemical protective clothing, including gloves, boots, chemical suiting, and full-face respirators, and all necessary precautions are taken to avoid spills and leaks during sampling and maintenance. Protective equipment is upgraded to include thermally protective gear when the material could be present at temperatures above 100º C.

2. Availability of Data for Members of Chemical Category and Analysis of Adequacy

Robust summaries of data available for all members of the category have been prepared, and are included in Appendix 1.

Table 1 documents the availability of SIDS endpoints and available/adequate data for members of the category. A complete dataset exists for the first member of the category, pentachloropyridine (2176-62-7), and for the fifth member of the category, tetrachloropyridine (2402-79-1). Physicochemical data for the remaining three single chemical category members were calculated where possible. Measured ecotoxicity data were available for one of the remaining single chemical category members (69045-78-9); data were calculated for another (17824-83-8). Measured data for acute mammalian toxicity endpoints were available for the three remaining single chemicals (1817-13-6, 69045-78-9, 17824-83-8). No measured data exist for the two category members which are process streams (68412-40-8, 70024-85-0), nor was calculation of data possible. However, the five single chemical category members are among the major components of the process streams, and some estimate of toxicity can be inferred from the single chemical category member data.

Table 1. Matrix of Available and Adequate Data on Chlorinated Pyridine Category Members							
Test	A. 2176-62-7	B. 1817-13-6	C.69045-78-9	D.17824-83-8	E. 2402-79-1	E. 68412-40-8	F. 70024-85-0
Physicochemical Properties							
Partition Coefficient	+	+[3]	[3]	[3]	+	-	-
Water Solubility	+	+[3]	[3]	[3]	+	-	-
Environmental Fate	+	+[3]	[3]	[3]	+	-	-
Biodegradation	+	+[3]	[3]	[3]	+	-	-
Environmental Transport	+	+[3]	[3]	[3]	[3]	-	-
Ecotoxicity							
Acute Fish	+	-	+	+[3]	+	-	-
Acute Daphnid	+[1]	-	+	+[3]	+	-	-
Alga	+	-	-	+[3]	+	-	-
Human Health Effects							
Acute	+	+	+	+	+	-	-
Repeated Dose	+	-[4]	[4]	-	+	-	-
Genotoxicity (*in vitro* – bacteria)	+	-	-	-	+	-	-
Genotoxicity (*in vitro* – non-bacterial)	+	-	-	-	-	-	-
Genotoxicity (*in vivo*)	+[2]	-	-	-	+	-	-
Repro/Developmental	+	-	-	-	+	-	-

+ = Data available and considered adequate; - = No data available or considered inadequate

[1]Although there are no data for daphnids, three other species of invertebrates were tested.

[2]USEPA guidance indicates that a combination of *in vitro* tests (e.g., bacterial plus rat lymphocyte chromosomal aberration) serve to satisfy the requirement for an *in vivo* test.

[3]Calculated values.

[4]Two two-week studies were summarized and deemed adequate with restrictions; however, no longer-term studies were located.

3. Comparison of Available Data for Category Members

Review of the data currently available on these compounds confirms the validity of this category, with similar/predictable activity in regard to physical/chemical properties, environmental fate, environmental effects and human health effects to be addressed in the EPA HPV Testing program. All data are summarized in IUCLID dossiers for individual category members, included as appendices to this document.

Data for category members were evaluated for patterns between endpoints. Table 2 documents values for physicochemical properties among category members. Calculated values are indicated as such.

Table 2. Comparison of Physicochemical Data for Category Members

Category Member	Partition Coefficient (log POW)	Water Solubility (mg/L @ 25ºC)	Vapor Pressure (mm Hg @ 25ºC)	Melting Point (ºC)	Environmental Fate (photolysis rate constant in cm^3/mol*sec)	Environ-mental Transport (% in air, water, soil, sediment)
A. 2176-62-7	3.53	8.5	0.014	125-126	1.1E-14[1]	73.55, 6.5, 19.5, 0.43[1]
B. 1817-13-6	4[1]	7.5[1]	0.0052[1]	47-48	1.39E-14[1]	32.9, 6.7, 59.1, 1.3[1]
C.69045-78-9	3.35[1]	99	0.0105[1]	52-54	4.77E-14[1]	17.9, 27.1, 53.8, 1.2[1]
D.17824-83-8	2.93	45[1]	3.30E-5[1]	150.5-151.5	2.8E-12[1]	1.5, 55.6, 41.9, 0.9[1]
E. 2402-79-1	3.32	22.6	0.2002	90.5	1.53E-14	18.9, 28.0, 51.9, 1.2[1]
F. 68412-40-8	ND	ND	ND	ND	ND	ND
G. 70024-85-0	ND	ND	ND	ND	ND	ND

ND = No Data
[1]Calculated value.

For the single chemical category members, partition coefficients are similar and range from about 3 to a maximum of 4, indicating a moderate potential for bioconcentration, as might be expected based on water solubility.

The single chemical water solubility values encompass a range from 7.5 to 99 mg/L, although solubility does not seem to be correlated either to partitioning within the aquatic environment or to toxicity (see discussion of aquatic toxicity studies). With the relatively low water solubilities noted, and given the fact that the materials in question do not ionize

at environmentally relevant pH, hydrolysis is not expected to be a significant factor in degradation.

All the single chemicals are low in vapor pressure, either estimated or measured values. Thus, as expected, the photolysis rate constants are very low for all single chemicals. There seems to be no basis for significant amounts of photodegradation for the category chemicals.

Fugacity values are similar for the chemicals within the category. With the exception of pentachloropyridine, which is calculated to favor partition to air, the single chemicals are calculated to distribute relatively evenly among water, air, and soil, with very little partitioning to sediment.

Thus, sufficient data are available for prediction of physicochemical properties for the category, and no further testing is needed.

Table 3. Comparison of Biodegradation Data for Category Members

Category Member	ThOD (mg/g substance)	BOD/COD	Biodegradation
A. 2176-62-7	0.64	ND	ND
B. 1817-13-6	ND	ND	Not readily biodegradable[1]
C.69045-78-9	ND	COD: 0.44 mg/mg BOD: 12% within 28 days	Not readily biodegradable[1]
D.17824-83-8	ND	ND	Not readily biodegradable[1]
E. 2402-79-1	ND	ND	50% within 95 days
F. 68412-40-8	ND	ND	ND
G. 70024-85-0	ND	ND	ND

ND = Not Determined
[1]Calculated value.

Table 3 documents a variety of biodegradation type data for chemicals within the category. Results from the studies consistently indicate a low potential for ready biodegradability, whether calculated or empirical data are considered. Thus, sufficient data are available for prediction of biodegradation for the category, and no further testing is needed.

Table 4. Comparison of Ecotoxicity Data (LC_{50}/EC_{50}) for Category Members			
Category Member	Acute Fish (mg/l)	Acute Invertebrate (mg/l)	Alga (mg/l)
A. 2176-62-7	0.47 (fathead minnow, 96 h) 1.23 (Emerald shiner, 72 h)	1.8 (shrimp, 43 h) >6 (soft-shell clam, 96 h) ND (*Tetrahymena pyriformis*) 0.4 ng/l[1]	2.03 (*Selenastrum capricornutum*, 96 h)
B. 1817-13-6	ND	0.1 mg/l[1]	ND
C.69045-78-9	>99 (fathead minnow, 96h)	>100 (*Daphnia magna*, 48 h) 0.1 mg/l[1]	ND
D.17824-83-8	26.0 (fish, calculated)	27.4 (*Daphnia sp*., calculated by EPA programs) 0.002 mg/l[1]	18.1 (alga, calculated)
E. 2402-79-1	1.5 (rainbow trout, 96 h)	2.05-2.14 (*D. magna*, 48 h)	8.8-14.1 (*S. capricornutum*, 120 h)
F. 68412-40-8	ND	ND	ND
G. 70024-85-0	ND	ND	ND
ND = Not Determined [1]Calculated value, TOPKAT® QSAR prediction for *Daphnia sp.*			

Table 4 documents ecotoxicity data for chemicals within the category. The aquatic toxicity of the single chemicals within this category appears to decrease with decreasing chlorination of the pyridine ring and increasing size of side chains to the pyridine ring. The most sensitive empirically derived endpoint for aquatic toxicity is that of the acute fish toxicity for pentachloropyridine, 0.47 mg/l, indicating a high level of toxicity. TOPKAT® prediction for invertebrates for this material is also low, 0.38 ng/l, as are TOPKAT predictions for other category members. Thus, all chemicals within the category may be considered potentially highly toxic to aquatic organisms. Considering that further testing would result in no increase in warnings, no further testing is needed.

Table 5. Comparison of Animal Toxicity Data for Category Members							
Category Member	Acute Toxicity				Repeated Dose Toxicity	Genetic Toxicity: In Vitro and In Vivo	Development Toxicity
	Acute Oral Toxicity	Dermal Irritation	Ocular Irritation	Dermal Sensitization			
A. 2176-62-7	•435 mg/kg (male rat, gavage) •126-1000 mg/kg (female rat, diet)	•Slight to moderate irritation (rabbit, 1 24-h application) •Burns (rabbit, repeated 24 h applications)	•Slight conjunctival irritation, resolved within 24 h	•Sensitizing (split adjuvant method)	•Kidney and liver effects (rat, 90-day, diet, NOAEL=10 mg/kg/day) •No effects (rat, 16-day, inhalation for 6 h, NOAEL=>1 ppm)	•Negative in bacterial reverse mutation assay (S. typhimurium TA98, TA100, TA1535, TA1537; E. coli WP2uvrA •Negative in rat lymphocyte chromosomal aberration assay •Negative in cytogenetic assay in mouse bone marrow	•Reduced fetal weight at maternally toxic dose levels (rat, developmental toxicity, gavage)
B. 1817-13-6	•1000-2000	• Slight to marked	•Moderate conjunctival	ND	•Liver effects (rat, 9-day,	ND	ND

	mg/kg (male rat, gavage)	irritation (rabbit, 1 24-h application) •Burns (rabbit, repeated 24 h applications)	and iridial irritation, slight corneal opacity, resolved within 48 h		inhalation for 6 h, NOAEL=0.32 ppm) •Liver effects (mouse, 9-day, inhalation for 6 h, NOAEL=0.32 ppm)		
C.69045-78-9	•500-1000 mg/kg (male rat, gavage)[1]	• Slight to moderate irritation (rabbit, 1 24-h application) •Burns (rabbit, repeated 24 h applications)	•Slight conjunctival irritation, very slight iridial irritation and corneal opacity, resolved within 48 h	•Sensitizing (modified Maguire method)	•Liver effects (rat, 2-week, inhalation for 6 h, NOAEL=1 ppm) •Liver effects (mouse, 2-week, inhalation for 6 h, NOAEL=1 ppm)	ND	ND
D.17824-83-8	•1000-2000 mg/kg (female rat, gavage) [2]	• Slight to moderate irritation (rabbit, 1 24-h application) •Burns	•Slight to moderate conjunctival irritation, resolved within 7 days[2]	ND	ND	ND	ND

		(rabbit, repeated 24 h applications)					
E. 2402-79-1	•1414 mg/kg (male rat, gavage) •1182 mg/kg (female rat, gavage) [3]	• Slight irritation (rabbit, repeated 24-h applications)	•Very slight conjunctival irritation, resolved within 1 h	•Not sensitizing (modified Maguire method)	•Kidney effects in males (rat, 91-day, diet, NOAEL=100 mg/kg/day) – hyaline droplet formation	•Negative in bacterial reverse mutation assay (S. typhimurium TA98, TA100, TA1535, TA1537 •Negative in mouse micronucleus assay	•No effects on offspring even at maternally toxic levels (rat, developmental/reproductive toxicity screen, IP injection)
F. 68412-40-8	ND	ND	ND	ND	ND	ND	ND
G. 70024-85-0	ND	ND	ND	ND	ND	ND	ND

ND = Not Determined

[1]An acute inhalation toxicity study also exists: LC50 > 114 ppm (male rat, 6 h)

[2]Single human exposures in an industrial setting have resulted in slight respiratory irritation, slight to moderate conjunctival irritation and slight to severe corneal injury.

[3]An acute inhalation toxicity study also exists: LC50 > 6300 ppm (male rat, 7 h)

Table 5 documents animal toxicity data for chemicals within the category.

Acute Toxicity: All single chemicals within the category are low to moderate in acute oral toxicity, with the lowest LD50 recorded being that for pentachloropyridine (2176-62-7) at 435 mg/kg in male rats via gavage. A range of values for the same chemical, 126-1000 mg/kg in female rats, encompasses the male rat value, but testing was conducted via a less commonly used route of exposure, inclusion in diet. Because no analyses of diet were conducted for this study, there is some uncertainty about calculated dose and therefore is considered valid with restrictions. However, the range specified still falls within the range of moderate toxicity. Other single chemicals in the category have oral LD50 values in the range of 500-2000 mg/kg via gavage. In addition, two single chemicals within the category, 2-chloro-5-trichloromethylpyridine (69045-78-9) and 3,4,5,6-tetrachloro-2-pyridine carbonitrile (17824-83-8) have inhalation LC50 values indicating a low to moderate level of toxicity consistent with the oral route of exposure. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) support the categorization of oral toxicity as moderate.

With regard to dermal irritancy potential, single chemical category members produce slight to moderate irritation with a single prolonged (24-hour) application, while repeated applications result in burns, with the single exception of 2,3,5,6-tetrachloropyridine, which did not produce burns upon repeated application. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) support the categorization of irritancy potential as slight to moderate.

Similar patterns for single chemical category members are seen in ocular irritancy studies, in which chemicals produce slight to moderate irritancy with no evidence of permanent impairment of vision. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) support the categorization of irritancy potential as slight to moderate.

Of the single chemical category members tested for potential to produce dermal sensitization, two (pentachloropyridine, 2176-62-7, and 2-chloro-5-trichloromethylpyridine, 69045-78-9) have produced evidence of dermal sensitization, while a third, 2,3,5,6-tetrachloropyridine, was negative in dermal sensitization testing under a modified Maguire method. Thus, category members should be regarded as having some level of potential to cause dermal sensitization. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) support the proposition of positive dermal sensitization potential.

With regard to acute toxicity, sufficient data exist to allow prediction of toxicity for category members, and thus no further testing is needed.

Repeated Dose Toxicity: Single chemical category members tested demonstrate effects on kidney and liver in rats and mice via both inhalation and dietary routes of administration in tests ranging from 9 to 90 days. The NOAEL for repeated dose toxicity for the various members of this category is consistent, and within a relatively narrow

range (0.32 to 1 ppm for inhalation studies, 10-100 mg/kg/day for dietary studies), based on a composite evaluation of all the repeated dose toxicity studies. These repeated dose toxicity studies have also reported a similar and common profile of target organs. Thus, the results of the collection of sub-chronic and chronic studies conducted on these substances are consistent and can be regarded as offering a true picture of repeated dose toxicity. With regard to repeated dose toxicity, sufficient data exist to allow prediction of toxicity for category members, and thus no further testing is needed.

Genetic Toxicity: Single chemical category members tested via both *in vitro* and *in vivo* genetic toxicity test methods have consistently produced negative results, indicating that these materials lack potential for genetic toxicity. Tests conducted include Ames assay both with and without metabolic activation, rat lymphocyte chromosomal aberration assay, mouse bone marrow cytogenicity assay, and mouse micronucleus assay. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) produce mixed results for mutagenicity potential, and thus must be considered carefully. With regard to genetic toxicity, sufficient data exist to allow prediction of toxicity for category members, and thus no further testing is needed.

Developmental Toxicity: Two category members, pentachloropyridine (2176-62-7) and tetrachloropyridine (2402-79-1), have been tested for potential to cause developmental toxicity. Pentachloropyridine produced evidence of reduced fetal weight only at maternally toxic dose levels, while tetrachloropyridine produced no evidence of developmental effects even at maternally toxic dose levels in a Chernoff test. As a conservative estimate, category members should be regarded as having potential to cause fetotoxicity at maternally toxic dose levels. Results of QSAR calculations using TOPKAT® and DEREK® (Table 5) support the extrapolation of ability to cause some level of developmental toxicity for at least one category member, 2-chloro-5-trichloromethylpyridine (69045-78-9). With regard to developmental toxicity, sufficient data exist to allow prediction of toxicity for category members, and thus no further testing is needed.

Table 5. Comparison of TOPKAT® and DEREK® QSAR Preditions for Category Members[a]								
Endpoints of Interest	A. 2176-62-7		B. 1817-13-6		C.69045-78-9		D.17824-83-8	
	T	D	T	D	T	D	T	D
Rat Oral LD50	77.8 mg/kg	NA	48.4 mg/kg	NA	195.6 mg/kg	NA	66.4 mg/kg	NA
Dermal Irritancy	+	-	-*	-	-*	-	-	-
Ocular Irritancy	+, Mild*	-	+. Moderate*	-	+. Moderate*	-	?	-
Dermal Sensitization	-*	+	+, Mild/Moderate*	-	+, Mild/Moderate*	-	+, Mild/Moderate*	+
Mutagenicity[b]	-	-	+*	+	+	+	+	-
Developmental Toxicity	-	-	-	-	+	-	-	-
Log P/Low KoW	4.06	NA	3.15	NA	2.81	NA	3.08	NA
Aerobic Biodegradability	-	NA	+	NA	-	NA	-	NA
Fathead minnow LC50	@	NA	@	NA	@	NA	@	NA
Daphnia LC50	381.6 ng/l	NA	64.1 µg/l	NA	515.9 µg/l	NA	1.7 µg/l	NA

[a]Because two of the category members (E. 68412-40-8 and F. 70024-85-0) are process streams for which component levels vary, no QSAR analysis could be conducted.

[b]TOPKAT® predicts results for the Ames' mutagenicity assay, while DEREK® predicts general mutagenicity results.

T = TOPKAT® results.

D = DEREK® results.

NA = Value not computed by the specified QSAR program.

+ = Probable

- = Improbable

? = Indeterminate

* = Accuracy can not be determined

@ = Error: Endpoint cannot be computed. No suitable submodel.

4. Conclusion

This test plan is expected to provide adequate data to characterize the human health effects and environmental fate and effects endpoints under the Program.

Evaluation of the chemicals in this category leads to the conclusions that [1] data currently exist to adequately represent the toxicological and ecological profile of major portions of this category, [2] there is a concurrence and similarity among the existing data for the various HPV/SIDS endpoints, supporting a single, continuous category, and [3] extrapolation from available data from previously conducted studies can be used to adequately represent most of the HPV/SIDS endpoints for individual members of the category. In addition, the nature of the chemical; the manner in which the chemical is manufactured, distributed, processed and used, the product stewardship measures taken to prevent exposure; and existing human/environmental data, indicate that our workers, the public and the environment are well protected from exposure to the chemicals within this category, and no further testing is needed.

REFERENCES

U.S. EPA . 1999. The use of structure-activity relationships (SAR) in the High Volume Chemical Challenge program, OPPT, EPA.